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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,194	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-65 and 68-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-65 and 68-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/17/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The amendment received 17 November 2005 has been entered in full. Claims 1-57, 66, and 67 are canceled. Claims 58-65 and 68-70 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

35 U.S.C. §§ 101 and 112, First Paragraph

Claims 58-65 and 68-70 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility, for reasons of record.

Claims 58-65 and 68-70 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for reasons of record.

Applicant's arguments (pp. 5-17, amendment of 17 November 2005) have been fully considered but are not found to be persuasive for the following reasons.

Applicant indicates that the gene amplification data of Example 114 are relied upon to support utility. Specifically, Applicant urges that the gene encoding PRO351 is amplified in at least ten o the lung tumor samples assayed. Applicant

points to the declaration of Dr. Goddard, filed under 37 CFR 1.132 on 20 May 2005, as stating that at least a 2-fold increase in gene copy number is significant, indicating that the gene can be used as a cancer diagnostic marker. As discussed in the previous Office Action (mailed 17 August 2005), while the data in Table 9 may provide a basis for utility and enablement of PRO351 nucleic acid, it does not provide a basis for utility or enablement of the claimed polypeptides. The art supports this position by establishing that there is no strong correlation between gene amplification and increased mRNA or protein levels. See Haynes et al., Pennica et al., Konopka et al. of record. Furthermore, the art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy before the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. The gene amplification assay does not provide a comparison between the lung tumor samples and normal lung epithelium, and thus it is not clear that PRO351 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO351 is a diagnostic probe for lung cancer unless it is clear that PRO351 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium. Also, while it might be argued in hindsight that PRO351 would still be a marker at least for precancerous, or damaged, lung epithelium, such is not suggested by the specification as originally filed and is not well-established in the *prior* art.

Furthermore, even if it could be established that gene amplification is reflected by increased polypeptide levels, the claims are broadly drawn to polypeptides that can be variants of the polypeptide of SEQ ID NO: 132, including fragments and substitution variants. One skilled in the art would expect that such variant sequences would not reasonably be expected to show changed levels for a particular disease state. Regarding the Goddard declaration, the claims are directed to polypeptides, not genes. A change in gene copy number does not reliably correlate with a change in polypeptide expression levels, as evidenced by the references cited herein. Furthermore, Table 9 reports a comparison of lung tumor tissue samples with a pooled sample of DNA from normal cells, but not matched tissue samples (i.e., normal lung epithelium tissue). The Goddard declaration states that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant. However, it is not clear if Dr. Goddard intended the phrase "normal samples" to include unrelated tissue samples such as those used in the specification. The art uses matched tissue samples as a rule when evaluating whether or not a protein can be used as a diagnostic for cancer, indicating that the art does not consider pooled, unrelated DNA samples to be an appropriate control. See Hu et al. (2003, Journal of Proteome Research 2:405-412) and Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313).

Applicant argues that the negative control taught in the specification was known in the art at the time of filing, and was accepted as a proper control in peer-reviewed journals. Applicant points to Pitti et al. and Bieche et al. as

evidence in support thereof. This has been fully considered but is not found to be persuasive. Both Pitti et al. and Bieche et al. did not rely solely upon the PCR assay using a control from blood genomic DNA to make conclusions. Pitti et al. also looked at northern blot analysis, ligand binding analysis, apoptosis induction analysis, and *in situ* hybridization analysis. Pitti et al. also ran an additional control in the PCR assays, using flanking DNA regions in tumor samples compared to blood DNA samples (p. 701, paragraph bridging the two columns). Bieche et al. relied upon Southern blotting to confirm the PCR results and note that not all samples showing PCR amplification also showed amplification by Southern blotting (p. 664, last paragraph before Discussion section). This was especially true for sequences that were amplified at low levels comparable to the levels that instant PRO351 was shown to be amplified. Finally, it is noted that publications have been cited as evidence that matched, cancer-free tissue samples are used as controls. See, for example, Hu et al. and Chen et al.

Applicant characterizes Hittelman et al., relied upon in the rejection as indicating that non-cancerous lung epithelium also has gene amplification, as supporting the asserted utility in that Hittelman et al. state that gene amplification would lead to diagnosis of a cancerous or pre-cancerous state (risk of cancer). This is not found to be persuasive because the specification does not assert that a positive result in the gene amplification assay indicates that the PRO clone assayed is useful as a diagnostic tool for *pre-cancerous* tissue or for *risk of cancer*. Rather, the specification indicates that a positive result in the assay indicates that the PRO clone can be used in the diagnostic determination of the

presence of cancers. Hittelman et al. provide evidence that a positive result can also correlate with damaged, but not cancerous, lung epithelium. Thus, further research would be required to reasonably confirm whether any particular PRO clone (nucleic acid) could be used as a diagnostic tool for cancer. Furthermore, it is important to keep in mind that the instant claims are not drawn to nucleic acids, but rather to polypeptides. As discussed on the record, gene amplification is not predictive of increased mRNA levels or increased polypeptide levels, and thus even if the nucleic acid were a marker, the polypeptides cannot be assumed to be so in the absence of evidence.

Applicant refers to Crowell et al. (1996, Cancer Epidermiol. Biomarkers Prev. 5:631-637) as further supporting the use of amplified genes as markers for assessing cancer risk. This has been fully considered but is not found to be persuasive. Again, the specification does not assert that PRO351 can be used as an indicator of increased risk of cancer. Also, Crowell et al. address nucleic acid probes, and do not extend their results to the use of polypeptide levels as diagnostic markers.

Applicant reiterates previous criticisms of Pennica et al. and Konopka et al., which are not found to be persuasive for reasons of record.

Applicant argues that the rejection does not establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Applicant argues that it is not legally required to establish a necessary correlation between the data presented and the claimed subject matter such that the amplification of every possible gene inevitably results in protein over-

expression. This has been fully considered but is not found to be persuasive. The art establishes that it is more likely than not that amplified gene levels or increased mRNA levels do not correlate with increased polypeptide levels. For example, Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and

protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Therefore, gene amplification data pertaining to PRO351 gene do not indicate anything significant regarding the claimed PRO351 polypeptides. The data do not support the specification's assertion that PRO351 polypeptides can be used as a cancer diagnostic agent or as a therapeutic drug development target. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO351 polypeptide is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent or therapeutic drug development target, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO351 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO351 **polypeptides** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides.

Applicant criticizes Haynes et al. by emphasizing that Haynes et al. shows a positive correlation between mRNA and protein amongst most of the 80 yeast proteins studied, and that very few data points deviated from the expected normal. This has been fully considered but is not found to be persuasive. Haynes et al. clearly conclude that, "even for a population of genes predicted to be relatively homogeneous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript" (p. 1863, section 2.1). This finding is reflected

in other references as well. Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977). Finally, Greenbaum et al. report a similar general lack of correlation. Thus, the evidence as a whole clearly indicates that one skilled in the art would not assume that an

increase in gene copy number would correspond with an increase in mRNA levels or protein levels without doing the empirical experimentation necessary to measure mRNA and protein levels. The requirement for such empirical experimentation indicates that the asserted utility for the claimed variant polynucleotides is not substantial; it is not in currently available form.

Applicant criticizes the Lian et al. publication by characterizing Lian et al. as being limited to differentiating myeloid cells and not to genes in general. Applicant also argues that Lian et al. use a very insensitive method of measuring protein. Applicant similarly criticizes Fessler et al. as being limited to a few proteins/RNAs stimulated by LPS and do not address genes in general. Applicant also states that Fessler et al. use an insensitive method of measuring proteins. This has been fully considered but is not found to be persuasive. Both Lian et al. and Fessler et al. do not limit their conclusions as being limited to the cell types studied, but rather extend their observations to mammalian cells in general. See also Greenbaum et al. (2003, Genome Biology 4:117.1-117.8). As discussed above, Greenbaum et al. caution against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in

human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Thus, the literature shows that those skilled in the art would not assume that increased mRNA levels are predictive of increased protein levels.

Applicant refers to Orntoft et al., Hyman et al., and Pollack et al. as supporting their position that gene amplification in cancer is predictive of elevated polypeptide levels. Specifically, Applicant argues that Orntoft et al. state that there is a highly significant correlation between mRNA and protein alterations in general, supporting Applicant's position. Applicant indicates that the examiner has mischaracterized Hyman et al., emphasizing that 44% of the highly expressed transcripts correlated with highly expressed proteins. This has been

fully considered but is not found to be persuasive. The preponderance of the totality of the evidence indicates that there is no general correlation between mRNA levels and polypeptide levels. See Greenbaum et al. (which considers Orntoft et al. and still concludes that there is poor correlation, in general, reported in the literature), Chen et al. (who found poor correlation between mRNA levels and polypeptide levels in lung cancer, which is directly on point for the instant fact pattern), and Hu e al., both of which look at large numbers of pairs of transcripts and polypeptides. Furthermore, Hyman et al. only looked at highly expressed mRNAs. There is no evidence that PRO351 mRNAs are elevated in lung cancers at all, let alone highly expressed. Also, since Hyman et al. found a correlation for 44% of the genes, it follows that it is more likely than not (56%) that even highly expressed transcripts do not correlate with elevated polypeptide levels. Thus, Hyman et al. supports the rejection even when evaluated by Applicant's characterization of the reference.

Applicant argues that the rejection incorrectly characterizes the PRO351 gene amplification data as "low" or "slight." Applicant refers to the Goddard declaration as evidencing that a 2.03 to 2.75-fold amplification is significant, and argues that the examiner has not provided any evidence to the contrary. This has been fully considered but is not found to be persuasive. It is maintained that the characterization is fair since a matched, non-cancerous tissue sample was not used as a control, the fact that gene amplification routinely occurs in precancerous lung epithelium is a documented phenomenon, no statistics were performed on the data, and the literature points to larger differences as

significant (e.g., Hu et al.). Moreover, even if it could be established that gene amplification is reflected by increased polypeptide levels, the claims are broadly drawn to polypeptides that can be variants of the polypeptide of SEQ ID NO: 132, including fragments and substitution variants. One skilled in the art would expect that such variant sequences would not reasonably be expected to show changed levels for a particular disease state. The evidence in the Goddard declaration is not commensurate in scope with the present claims.

Applicant argues that Orntoft et al., Hyman et al., and Pollack et al. were submitted as evidence that gene amplification is generally predictive of increased mRNA levels, and the Polakis declaration was submitted as evidence that increased mRNA levels generally correlates with increased polypeptide levels. Applicant argues that the examiner must accept the opinion of an expert, and the suggestion that Dr. Polakis might be misrepresenting experimental results is inappropriate. This has been fully considered but is not found to be persuasive. The merits of Orntoft et al., Hyman et al. and Pollack et al. have been thoroughly discussed on the record, and strong counter evidence has been submitted. Regarding the Polakis declaration, the examiner never intended to indicate that Dr. Polakis misrepresented data. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene

amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) There is strong opposing evidence showing that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., and Greenbaum et al. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. This is not to imply that any misrepresentation has occurred. (4) Finally, Dr. Polakis refers to facts; however, the data are not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly over-expressed were the genes that correlated with increased polypeptide levels? Without such details, it is difficult to determine how relevant the data were to the instant fact pattern.

Applicant argues that the central dogma of molecular biology is that there is a correlation between mRNA levels and polypeptide levels, and that the literature merely reports some examples that are exceptions. Applicant argues that, in the majority of amplified genes, gene amplification leads to increased mRNA production and increased polypeptide levels. Applicant refers to Orntoft

et al., Hyman et al., Pollack et al., and the Polakis declaration in support of their conclusion. Applicant argues that the skilled artisan would conclude that the claimed PRO351 polypeptides have utility in cancer diagnosis. This has been fully considered but is not found to be persuasive. First, PRO351 genomic DNA was found to be amplified in lung cancer samples compared to a normal DNA control from blood. Gene amplification in lung tumors was not compared to a matched normal tissue sample, as is the standard in the art (see Pennica et al., Konopka et al., Hu et al., Chen et al.). The data were not corrected for aneuploidy, which was known to be common in cancerous and non-cancerous lung tissue (see Sen, 2000, Curr. Opin. Oncol. 12:82-88; Hittelman, 2001, Ann. NY Acad. Sci. 952:1-12). Thus, it is not clear from the gene amplification data whether or not PRO351 genomic DNA actually is amplified in certain lung tumors. Second, the literature reports that gene amplification does not reliably correlate with increased mRNA levels (see Pennica et al., Konopka et al.). Third, the literature reports that increased mRNA levels do not correlate with increased polypeptide levels in healthy tissue (see Haynes et al., Gygi et al., Lian et al., Fessler et al.) or cancerous tissue (see Hu et al., LaBaer, Chen et al., Hanna et al.). In view of the totality of the evidence, the skilled artisan would not reasonably presume that PRO351 polypeptide is overexpressed in certain lung tumors based on the disclosure regarding gene amplification without actually testing for PRO351 polypeptide overexpression. The requirement for such testing indicates that the asserted utility is not substantial, i.e., it is not in currently

available form. In view of the totality of the evidence, the rejections for lack of utility and enablement are proper.

Applicant criticizes Hu et al. Specifically, Applicant characterizes Hu et al. as being limited to estrogen-receptor-positive breast tumor only. Applicant criticizes the types of statistical tests performed by Hu et al. Applicant concludes that, based on the nature of the statistical analysis performed in Hu et al., and the fact that Hu et al. only analyzed one class of genes, the conclusions drawn by the examiner are not reliably supported. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptides is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO351

mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO351 protein can be used as a cancer diagnostic. Furthermore, Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. Also, Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas (the same type of cancer for which PRO351 tested positive). Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). The instant specification does not provide additional information regarding whether or not PRO351 mRNA or polypeptide is overexpressed in lung adenocarcinomas, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Regarding Applicant's criticism of Hu et al.'s statistical analysis, Applicant is holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc. Regarding Applicant's criticism of Hu et al. as being

limited to a specific type of breast tumor, Hu et al. is cited as one of several pieces of evidence that gene amplification in a tumor does not correlate with mRNA overproduction or protein overproduction. When viewed with the evidence of record as a whole, there is no correlation between gene amplification, mRNA levels and protein levels. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

Applicant argues that the examiner has misread Hanna et al., in that Hanna et al. state that gene amplification and polypeptide expression are well-correlated, and that only a subset of tumors show discordant results. This has been fully considered but is not found to be persuasive. The preponderance of the totality of the evidence indicates that it is more likely than not that gene amplification correlates with increased expression of polypeptide. Hanna et al. constitutes additional evidence that the skilled artisan would not assume that gene amplification correlates with polypeptide over-expression, but would empirically test for polypeptide over-expression.

Applicant argues that the PRO351 gene is amplified in ten lung tumors, similar to the HER-2/neu gene of Hanna et al. Applicant argues that the majority of amplified genes correlate with increase polypeptide expression. Applicant argues that even if an amplified gene did not correlate with an overexpressed encoded protein, the protein would still have a credible, specific, and substantial asserted utility. Applicant points to the declaration of Dr.. Ashkenazi, submitted under 37 CFR 1.132 on 29 April 2004, as establishing that, even if the protein

were not overexpressed, the simultaneous testing of gene amplification and gene product overexpression would enable more accurate tumor classification. Applicant concludes that such a situation would allow for better tumor classification and better determination of suitable therapy. This has been fully considered but is not found to be persuasive. The specification does not disclose such further testing of gene product overexpression. Therefore, the skilled artisan would have been required to do the testing to reasonably confirm whether or not the PRO351 polypeptide is overexpressed. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public. Furthermore, the specification provides no assertion that the claimed PRO351 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO351. For example, neither the specification nor the prior art discloses an agent that targets PRO351 that is useful for cancer therapy. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial.

Applicant argues that the claimed variant polypeptides are enabled because the claims require that the nucleic acid encoding the polypeptide is amplified in lung tumors, and the claims require the polypeptides to be native sequence polypeptide variants. Applicant argues that many polypeptides, especially tumor antigens, are known to have isoforms or variants, citing Peng et al., Kiss et al., Perego et al., Nagao et al., and Hong et al. in support thereof.

Applicant argues that the specification provides ample guidance for the skilled artisan to identify variants encompassed by the claims. This has been fully considered but is not found to be persuasive. "Make and test" is not the standard for enablement. Factors to be considered in determining whether a disclosure enables one skilled in the art to make and use the claimed invention in its full scope without resorting to undue experimentation include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature or complexity of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. See *In re Wands*, 8 USPQ2d. 1400 (Fed. Cir. 1988). In this case, a great deal of experimentation is required to determine which, if any, of the polypeptides embraced by the large scope of the claims is actually encoded by a nucleic acid that is over-expressed in any type of lung tumor cells, as each variant must be tested empirically. There is no guidance as to which variants would be expected to be encoded by nucleic acids that were over-expressed in tumors, and which ones would not. There are no working examples directed to any PRO351 polypeptides, variant or not. The nature of the invention is extremely complex, involving large numbers of polypeptides and complex disease states. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical

reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). In this case, not even a single embodiment has been enabled. The art is unpredictable, since even minor mutations can be associated with cancerous or healthy tissue. Empirical experimentation is necessary to determine which isoforms are associated with cancer. See Kiss et al. (2004, Anticancer Research 24:3965-70, cited by Applicant), and other references cited by Applicant. Finally, the claims are quite broad, encompassing a genus of structures that can differ as much as 20% from the reference sequence, each of which can be encoded by an enormous number of degenerate nucleic acid sequences, each of which would have to be tested for over-expression in lung tumor cells. In view of all of these factors, undue experimentation would have been required of the skilled artisan to make and use the claimed invention. The instant claims do not recite a functional limitation of the polypeptides themselves, but rather for the encoding nucleic acids. Therefore, it is not clear how the skilled artisan is to use the claimed polypeptides themselves.

Claims 58-62, 69 and 70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons of record.

Applicant's arguments (pp. 17-21, amendment of 17 November 2005) have been fully considered but are not found to be persuasive for the following reasons.

Applicant reviews the legal standard for written description, with which the examiner takes no issue.

Applicant argues that the specification reduces to practice the full-length polypeptide of SEQ ID NO: 132, with or without its signal sequence. Applicant urges that the genus of polypeptides at least 80% identical to SEQ ID NO: 132 which possess the functional property of being encoded by a nucleic acid that is amplified in lung tumors are adequately described. This has been fully considered but is not found to be persuasive. The claims do not actually recite a functional property of the genus of polypeptides, but rather recite a feature of the encoding nucleic acids. Such does not impart any function to the encoded polypeptides.

Applicant argues that the specification describes methods for making variant polypeptides and calculating percent identity. Applicant urges that the specification provides detailed guidance regarding what changes can be made to a PRO polypeptide without adversely affecting its activity. Applicant also points to the specification's disclosure of methods for identifying polypeptides as recited in the claims, as well as Example 114. This has been fully considered but is not found to be persuasive. "Make and screen" is not the legal standard for adequate written description under 35 U.S.C. § 112, first paragraph. As was set forth in *Fiers v. Revel*, 25 USPQ2d 1601 (CAFC 1993) and *Amgen Inc. v. Chugai*

Pharmaceutical Co., Ltd., 18 USPQ2d 1016, adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The compound itself is required.

Applicant argues that the instant fact pattern is distinguished from that in *Fiers v. Revel* and *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.* in that the court decisions involved nucleic acids wherein the instant claims are directed to polypeptides. This has been fully considered but is not found to be persuasive, because the instant polypeptides are defined by their encoding nucleic acids. A genus of nucleic acids that are amplified in lung tumors and that encode polypeptides that are sequence variants of SE ID NO: 132 have not been described in the instant specification. Therefore, *Fiers v. Revel* and *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.* are directly on point.

Applicant argues that the instant fact pattern is consistent with *Enzo Biochem., Inc. v. Genprobe, Inc.*, 296 F.3d 1316 (Fed. Cir. 2002) and the USPTO's written description guidelines. Applicant argues that case law holds that a description of a combination of structural and functional features may be relied upon as meeting the requirements of 35 U.S.C. § 112, first paragraph. This has been fully considered but is not found to be persuasive. The claims encompass a genus of polypeptides that are defined by structure only. The recitation that the polypeptides are encoded by nucleic acids that are amplified in lung tumors does not impart an activity limitation on the polypeptides themselves. There is no test that can be performed on a polypeptide to determine properties

of its nucleic acid. Also, there is no way in which a polypeptide that is encoded by such a nucleic acid can be used differently from a polypeptide which is not.

Applicant argues that the instant claims reflect the fact pattern presented in Example 14 of the USPTO's written description guidelines, and thus should be found to meet the requirements of 35 U.S.C. § 112, first paragraph. This has been fully considered but is not found to be persuasive. The instant claims differ from those in Example 14 in two significant ways. First, the claims encompass variant polypeptides that are much more divergent from the reference sequence than those of Example 14. (Example 14 indicates that 95% identity is acceptable under certain circumstances whereas the instant claims encompass polypeptides that are only 80% identical). Second, Example 14 indicates that the polypeptides themselves have a specific activity. In the instant case, the claimed variants polypeptides are not themselves required to have a functional property. Only the encoding DNA is recited as having a particular feature, as discussed above.

Therefore, based upon the preponderance of the totality of the evidence, the rejection is properly maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.**

See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D. can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ECK

ELIZABETH KEMMERER
PRIMARY EXAMINER